WE CLAIM :

1. An improved process for preparation of Levofloxacin hemihydrate having single individual impurity not more than 0.1 % and free from particulate matter & from the other enantiomer (R-form) which comprises
   i. dissolving levofloxacin technical grade in aqueous alkaline solution,
   ii. treating the resulting solution with activated carbon at room temperature,
   iii. removing the undissolved particulate matter filtration,
   iv. bringing the pH of the aqueous alkaline levofloxacin solution to neutral using dilute mineral acid,
   v. removing the precipitated particulate matter by filtration,
   vi. acidifying the resulting solution,
   vii. treating the acidified solution with activated carbon at room temperature,
   viii. filtering the undissolved particulate matter by filtration,
   ix. neutralizing the acidic solution,
   x. filtering again to remove any particulate matter present and,
   xi. extracting the resulting product with chlorinated solvent and concentrating under vacuum using aqueous tetrahydrofuran or in admixture with other organic solvents to get highly pure levofloxacin hemihydrate having single individual impurity less than 0.1% and free from particulate matter & from the other enantiomer (R-form).

2. An improved process as claimed in claim 1 wherein the filtration in steps (viii) & (x) may be effected using a 0.2 micron filter.

3. An improved process as claimed in claims 1 & 2 wherein the alkaline Levofloxacin solution is stirred at a pH in the range of 8.0 to 12.0, preferably 10.0-12.0, more preferably 11.0-11.5.

4. An improved process as claimed in claims 1 to 3 wherein the alkali used is selected from sodium hydroxide or potassium hydroxide, preferably sodium hydroxide and the concentration of the solution is 5 to 20% preferably 8-10%.

5. An improved process as claimed in claims 1 to 4 wherein the pH is brought to 7.0-7.5 using dilute hydrochloric acid, preferably 0.5N to 5N hydrochloric acid, more preferably 1N hydrochloric acid.

6. An improved process as claimed in claims 1 to 5 wherein the precipitated particulate matter is filtered and the pH is adjusted to 3.0-6.0 preferably 4.0 to 5.5 more preferably 4.5-5.0 using glacial acetic acid.

7. An improved process as claimed in claims 1 to 6 wherein the aqueous acidic levofloxacin solution is treated with activated carbon at room temperature and the clear solution is filtered the pH to neutral preferably 7.0-7.5 using dilute aqueous ammonia solution.

8. An improved process as claimed in claims 1 to 7 wherein the neutral aqueous solution is again filtered and extracted with chlorinated solvent preferably methylene chloride.

9. An improved process as claimed in claims 1 to 8 wherein the extract is concentrated under vacuum (600-650 mm of Hg) below 40°C.and the resulting residue is concentrated after stirring with tetrahydrofuran or its mixture with any other organic solvent.

10. An improved process as claimed in claims 1 to 9 wherein the residue is slurred with 1-5% aqueous tetrahydrofuran preferably with 2-2.5% aqueous tetrahydrofuran.

11. An improved process as claimed in claims 1 to 10 wherein the slurring with tetrahydrofuran is effected at 40-70°C preferably at 50-60°C more preferably at 58-60°C.

12. An improved process as claimed in claims 1 to 11 wherein the slurring with tetrahydrofuran is effected for a period in the range of 30 minutes to 2 hours preferably 30 minutes to 1 hour and then cooled to -5 to 15°C preferably 0-5°C and stirred for 30 minutes to 2 hours preferably 1 hour to 1 hour 30 minutes.

13. An improved process as claimed in claims 1 to 12 wherein the product is filtered and suck dried for 15 minutes to 1 hour preferably 30 minutes to 45 minutes and the product was dried at 50-80°C preferably at 70-75°C for 2 to 7 hours preferably 4-6 hours more preferably 5 to 5 hours 30 minutes.

14. An improved process for the preparation of Levofloxacin hemihydrate which comprises,

i. Converting 2,3,4,5-tetrafluoro benzoic acid to its acid chloride by conventional method to give the diethyl-2,3,4,5-tetrafluoro benzoyl malonate.

ii. Partially hydrolyzing and decarboxylating the resulting diethyl-2,3,4,5-tetrafluoro benzoyl malonate by conventional methods to give ethyl-2,3,4,5-tetrafluoro benzoyl acetate.

iii. Converting the ethyl-2,3,4,5-tetrafluoro benzoyl acetate by known methods to ethyl-2-(2,3,4,5-tetrafluoro benzoyl)-3-ethoxy acrylate.

iv. Condensing the ethyl-2-(2,3,4,5-tetrafluoro benzoyl)-3-ethoxy acrylate obtained in step (iii) with (S)-2-amino-1-propanol in a solvent, to give ethyl-2-(2,3,4,5-tetrafluoro benzoyl)-3-[(1-hydroxy prop-2(S)-yl) amino] acrylate,

v. Cyclising the resulting ethyl-2-(2,3,4,5-tetrafluoro benzoyl)-3-[(1-hydroxy prop-2(S)-yl) amino] acrylate by conventional methods to give (S)-ethyl-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate and,

vi. further hydrolyzing (S)-ethyl-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate,obtained in step (v) by known methods to give (S)-9,10-difluoro-2,3-dihydro-3-methyl-7-oxo-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (namely Levofloxacin Q-acid),

vii. converting the Levofloxacin Q-Acid by condensing with N-methyl piperazine by using solvent or without using solvent by any known methods to (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (namely Levofloxacin technical),

viii. dissolving levofloxacin technical in aqueous alkaline solution,

ix. treating the resulting solution with activated carbon at room temperature,

x. removing the undissolved particulate matter by filtration,

xi. bringing the pH of the aqueous alkaline levofloxacin solution to neutral using dilute mineral acid,

xii. removing the precipitated particulate matter by filtration,

xiii. acidifying the resulting solution,

xiv. treating the acidified solution with activated carbon at room temperature,

xv. filtering the undissolved particulate matter by filtration,

xvi. neutralizing the acidic solution,

xvii. filtering again to remove any particulate matter present and,

xviii. extracting the resulting product with chlorinated solvent and concentrating under vacuum using aqueous tetrahydrofuran or in admixture with other organic solvents to get highly pure levofloxacin hemihydrate having single individual impurity not more than 0.1% and free from particulate matter & from the other enantiomer (R-form).

15. An improved process as claimed in claim 14 wherein in step (i) , Diethyl malonate is acylated using 2,3,4,5-tetrafluoro benzoyl chloride in the presence of magnesium, ethanol by making diethyl ethoxymagnesiomalonate.

16. An improved process as claimed in claims 14 & 15 wherein in step (ii) the conversion is effected using an aqueous medium employing catalytic amount of para toluene sulfonic acid.

17. An improved process as claimed in claims 14 to 16 wherein in the reagents used for the condensation in step (iii) is triethyl orthoformate and acetic anhydride.

18. An improved process as claimed in claims 14 to 17 wherein the solvent used in step(iv) is methylene chloride.

19. An improved process as claimed in claims 14 to 18 wherein the cyclisation in step (v) is done in the presence of suitable base such as potassium carbonate and an aprotic solvent such as N, N-dimethyl formamide.

20. An improved process as claimed in claims 14 to 19 wherein the hydrolysis in step (vi) is carried out using acetic acid and dilute hydrochloric acid.

21. An improved process as claimed in claims 14 to 20 wherein, the condensation in step (vii) is carried out either using aprotic solvent or without using solvent.

22. An improved process as claimed in claim 21 wherein, the aprotic solvent which is used for condensation is pyridine.

23. An improved process as claimed in claims 14 to 21 wherein the filtration in steps (xv) & (xvii) may be effected using a 0.2 micron filter.

24. An improved process as claimed in claims 14 to 23 wherein the alkaline Levofloxacin solution is stirred at a pH in the range of 8.0 to 12.0, preferably 10.0-12.0, more preferably 11.0-11.5.

25. An improved process as claimed in claims 14 to 24 wherein the alkali used in step (viii) is selected from sodium hydroxide or potassium hydroxide, preferably sodium hydroxide and the concentration of the solution is 5 to 20% preferably 8-10% .

26. An improved process as claimed in claims 14 to 25 wherein the pH is brought to 7.0-7.5 using dilute hydrochloric acid, preferably 0.5N to 5N hydrochloric acid, more preferably 1N hydrochloric acid.

27. An improved process as claimed in claims 14 to 26 wherein the precipitated particulate matter is filtered and the pH is adjusted to 3.0-6.0 preferably 4.0 to 5.5 more preferably 4.5-5.0 using glacial acetic acid.

28. An improved process as claimed in claims 14 to 27 wherein the aqueous acidic levofloxacin solution is treated with activated carbon at room temperature and the clear solution is filtered the pH to neutral preferably 7.0-7.5 using dilute aqueous ammonia solution.

29. An improved process as claimed in claims 1 4to 28 wherein the neutral aqueous solution is again filtered and extracted with chlorinated solvent preferably methylene chloride.

30. An improved process as claimed in claims 14 to 29 wherein the extract is concentrated under vacuum (600-650 mm of Hg) below 40°C.and the resulting residue is concentrated after stirring with tetrahydrofuran or its mixture with any other organic solvent .

31. An improved process as claimed in claims 14 to 30 wherein the residue is slurred with 1-5% aqueous tetrahydrofuran preferably with 2-2.5% aqueous tetrahydrofuran.

32. An improved process as claimed in claims 14 to 31 wherein the slurring with tetrahydrofuran is effected at 40-70°C preferably at 50-60°C more preferably at 58-60°C.

33. An improved process as claimed in claims 14 to 32 wherein the slurring with tetrahydrofuran is effected for a period in the range of 30 minutes to 2 hours preferably 30 minutes to 1 hour and then cooled to -5 to 15°C preferably 0-5°C and stirred for 30 minutes to 2 hours preferably 1 hour to 1 hour 30 minutes.

34. An improved process as claimed in claims 14 to 33 wherein the product is filtered and suck dried for 15 minutes to 1 hour preferably 30 minutes to 45 minutes and the product was dried at 50-80°C preferably at 70-75°C for 2 to 7 hours preferably 4-6 hours more preferably 5 to 5 hours 30 minutes.

35. An improved process for the preparation of Levofloxacin hemihydrate having single individual impurity not more than 0.1 % and free from particulate matter & from the other enantiomer (R-form) from Levofloxacin technical substantially as herein described with reference to the Examples 1 & 2

36. An improved process for the preparation of Levofloxacin hemihydrate having single individual impurity not more than 0.1 % and free from particulate matter & from the other enantiomer (R-form) from 2,3,4,5-tetrafluoro benzoic acid substantially as herein described with reference to the Example 3.

For NEULAND LABORATORIES LIMITED

CHAIRMAN & MANAGING DIRECTOR

- 6 NOV 2004